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Cystic Kidneys Associated With Connective Tissue Disorders

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Advances in molecular genetics have resulted in the identification of several forms of autosomal dominant polycystic kidney disease (PKD). Cystic kidneys have also been observed in tuberous sclerosis, von Hippel-Lindau syndrome, oro-facial-digital type I syndrome, Hajdu-Cheney syndrome, Ehlers-Danlos syndrome, and an "overlap" connective tissue disorder, and cannot be distinguished by ultrasonography from PKD. We have studied four children with similar cystic kidneys. None had a family history of PKD. One child has osteogenesis imperfecta type IV, two appeared to have a mild Ehlers-Danlos syndrome, and the fourth has inguinal hernias and undescended testes. We speculate that polycystic kidneys may occur in connective tissue dysplasias. We also realize that these may be chance associations with spontaneous mutations for PKD. Am. J. Med Genet. 69: 133–137, 1997. © 1997 Wiley-Liss, Inc.

KEY WORDS: polycystic kidneys; osteogenesis imperfecta; connective tissue disorder; Ehlers-Danlos syndrome

INTRODUCTION

Cystic kidneys in infants and children that resemble autosomal dominant polycystic kidney disease (PKD) can be divided into non-syndromal and syndromal PKD [Kaplan et al., 1995]. In about 95% of families with non-syndromal PKD the gene (PKD1) is linked to 16p13.3 [Reeders et al., 1985]. A second gene locus (PKD4) is found in about 5% of families with the same clinical phenotypes as PKD1 [Kimberling et al., 1988; Bachner et al., 1991; Fossdal et al., 1993]. Linkage has been established to a locus at chromosome 4q13-23 [Kimberling et al., 1993; Peters et al., 1993]. There is evidence for a third locus for PKD in one family [Daoust et al., 1995]. Syndromal PKD occurs in tuberous sclerosis [Bernstein and Kissane, 1986; Kandt et al., 1992], von Hippel-Lindau syndrome [Lamiell et al., 1980; Frimodt-Moller et al., 1981], the oro-facial-digital syndrome type I [Kennedy et al., 1991; Salinas et al., 1991], and Hajdu-Cheney syndrome [Rosenmann et al., 1977; van den Houten, 1985; Zahram, 1984; Exner, 1988; Kaplan et al., 1995]. PKD has also been reported in two cases of Ehlers-Danlos syndrome [Lewitus, 1956; Imahori et al., 1969]. In addition, Somlo et al. [1993] reported a kindred with PKD1 and a connective tissue disorder similar to Marfan syndrome.

We describe four unrelated patients with sporadically occurring cystic kidneys with ultrasonographic features similar to those of PKD. None had evidence of autosomal recessive polycystic kidney disease, tuberous sclerosis, von Hippel-Lindau, oro-facial-digital type I, or Hajdu–Cheney syndromes. Three had systemic connective tissue disorders: one had osteogenesis imperfecta type IV and two appeared to have mild Ehlers-Danlos syndrome. The fourth patient had inguinal herniae and undescended testes. We propose that in some patients PKD may be part of multisystem connective tissue disorders.

CLINICAL REPORTS

Patient 1 (D.K. DOB 10/28/82)

This boy was born after a normal pregnancy and was delivered by cesarean section at 38 weeks of gestation for a disproportionately large head. Renal ultrasound examinations were done yearly because he had somatic asymmetry. At 8 years osteogenesis imperfecta was diagnosed on the basis of short stature (<5th centile), relatively large head (OFC <95th centile), triangular face, blue sclerae, brown teeth, thin scars, and four previous fractures of skull, femur, clavicle, and radius.

Family history. There was no family history of renal disease or osteogenesis imperfecta. Renal ultrasonograms were done on the mother at age 32 years and on the father at age 37 years. No cysts could be detected in the kidneys of either parent.

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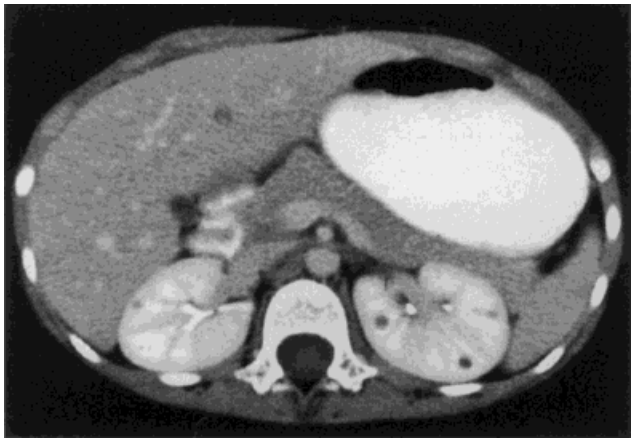

Fig. 1. Contrast-enhanced CT scan (patient 1, age 7 years). Axial sections at two different levels of the kidneys demonstrate bilateral renal cysts.

Laboratory studies. Renal function was normal; urine dipstick analysis showed microscopic hematuria and proteinuria. An audiogram was normal.

Imaging studies. No abnormalities were detected on serial ultrasonograms done from 5 months to 5 years. A small cyst was noted in the upper pole of the right kidney at 5 years. At 7 years several cysts were detected by ultrasonography in the medulla, cortico-medullary junction and cortex of both kidneys. The kidneys were normal in size and there was no evidence of renal tubular ectasia. The liver and spleen appeared normal. CT scan of the abdomen was done at 8 years (Fig. 1). Five millimeter images were obtained throughout the kidneys with and without contrast medium. There was normal perfusion of both kidneys which were normal in size, position and shape. Numerous cysts were seen throughout cortex and medulla in both kidneys. The largest measured 1 cm and was located in the right renal hilum. The cysts did not fill with contrast medium. The liver appeared homogenous and there were no cysts in liver, pancreas, or spleen.

Collagen studies. Collagen studies of cultured skin fibroblasts (done by Peter Byers M.D., Ph.D.) were consistent with type IV osteogenesis imperfecta. The cells synthesized and secreted one normal and one abnormal form of type I collagen.

Patient 2 (T.B. DOB 7/12/84)

This boy was noted at birth to have bilateral abdominal masses and renal ultrasonography documented cystic kidneys. At 6 weeks he had a pylorotomy for treatment of pyloric stenosis and a liver biopsy was performed. There was no evidence of congenital hepatic fibrosis. At 6 months his blood pressure was 150/110 mm Hg. At 8 years height was on the 75th centile and weight was on the 50th centile. Blood pressure, on treatment with an ACE-inhibitor, was 114/67 mm Hg.

He had decreased subcutaneous tissue and visible veins on the chest. There was slightly increased mobility of the distal interphalangeal joints, elbows, and knees. The ears, but not the skin, were hyperextensible. A scar on the abdomen was wide and slightly heaped. He had mild pectus excavatum and clinodactyly of 5th fingers. There were no features of any known syndrome associated with PKD.

Family history. Two of the mother's cousins, age 40 and 45 years, had intracranial aneurysms. A 26-year brother had pyloric stenosis in infancy, is 193 cm tall, double-jointed, dislocates his thumb, and is thin. He does not have easy bruising.

Imaging studies. A sonogram was done at age 1 day. Both kidneys were enlarged. The length of the left kidney was 9.4 and of the right 7 cm. Numerous cysts were seen in each kidney. At 5 years the kidneys and the cysts had increased in size (Fig. 2).

Patient 3 (K.B. DOB 12/18/88)

This girl was the product of a normal, term pregnancy and weighed 3 kg. At 11 years she had dark red, macroscopic hematuria for 3 days. There was no burning on micturition. She complained of left costovertebral angle pain. Height was 152.7 cm (75th centile) and weight 36.7 kg (75th centile). Blood pressure was 111/69 mm Hg. There were no minor anomalies. She had mildly increased flexibility of all joints, thin wide scars, slight extensibility of ears, and easy bruisability. She did not have blue sclerae, fractures, scoliosis, thin skin, or visible veins. Cardiac findings were normal.

Laboratory studies. The BUN was 11 mg/dl and serum creatinine was 0.8 mg/dl. Serum electrolyte concentrations were normal. The hemoglobin was 8.2 g/dl. Urinalysis was negative for protein and 1+ for blood transiently.

Family history. Neither parent had evidence of polycystic kidneys on renal ultrasonograms at age 38 and 40 years. The paternal grandmother had a cerebro-vascular accident at 40 years and died at 60 years with an infarction in the posterior fossa. There was no history of hypertension or renal disease. The

Fig. 2. Sonogram of the kidneys of patient 2 at age 5 years. The kidneys are large and there are numerous, large cysts in each kidney. A small amount of parenchyma is still seen between the cysts.

proposita's sister, age 9 years, had mild joint laxity. The patient and her father had thalassemia minor.

Imaging studies. Ultrasound examinations demonstrated cysts in both kidneys (Fig. 3a,b). A parapelvic cyst was seen in the left kidney. CT scan showed several small cysts in the right kidney and a large parapelvic, contrast-filled cyst in the left kidney.

Treatment. The left kidney was explored surgically. Numerous cysts were visible on the surface. The parapelvic cyst was incised, drained, fulgurated with an argon beam laser, and over-sewn. The kidney was biopsied but no abnormalities were seen histologically.

Collagen studies. Results of collagen studies of cultured skin fibroblasts (done by Peter Byers M.D., Ph.D.) were normal.

Patient 4 (B.C. DOB 4/30/91)

This boy was born 2 weeks post-term after a normal pregnancy. Birth weight was 3.1 kg. He had bilateral inguinal hernias, very large hydroceles, and intra-abdominal, tubular shaped testes. At 2 months he was noted to have a protuberant abdomen. He did not have any minor anomalies and his urethra was normal. Blood pressure was 92/65 mm Hg. At 1 year both kidneys were palpable.

Family history. There were no sibs and no abortions. There was no family history of renal disease. Renal ultrasonograms done on the mother at age 35 years and the father at 31 years were normal.

Laboratory studies. Urinalysis was negative for protein and blood. The BUN was 18 mg/dl and serum creatinine was 0.3 mg/dl. The serum electrolyte concentrations were normal.

Imaging studies. At age 1 month a sonogram demonstrated large and hyperechogenic kidneys. There were small anechoic lesions in the kidneys. At 5 years numerous cysts were clearly visible within each kidney (Fig. 4).

DISCUSSION

These patients have findings resembling those of PKD by ultrasonography, and apparent connective tissue disorders. Criteria for the diagnosis of PKD are at least one cyst in each kidney or two or more cysts in one kidney by ultrasonography [Bear et al., 1992], and a family history of an affected parent or grandparent. Simple cysts must be considered in the differential diagnosis. Our patients did not have simple cysts which are usually solitary [Gordon et al., 1979]; bilateral simple cysts are uncommon in children [Bear et al., 1992].

Our patients did not have an affected parent or grandparent; this causes difficulties in precise diagnosis and classification. Most patients with PKD, designated PKD1, have linkage with RFLP markers on the short arm of chromosome 16 [Reeders et al., 1985; Gabow, 1991; Bear et al., 1992]. In about 5% of patients with the phenotype of PKD without linkage to the locus on chromosome 16 have PKD2 which is linked to 4q13–23 [Kimberling et al., 1993; Peters et al., 1993]. In addition, Daoust et al. [1995] have reported a family in which PKD was not linked to chromosome 16p or 4q.

Because our patients did not have an affected parent with PKD it was not possible to use restriction length polymorphisms as an aid to diagnosis. There is a low likelihood (5%) that they had PKD because only 11% of persons at 50% risk before age 30 years have cysts [Bear et al., 1992]. It is possible that each of these patients had a spontaneous mutation for PKD or that there was reduced penetrance of the gene(s) for PKD [Bachner et al., 1991]. PKD is the commonest dominantly inherited renal cystic disorder in humans with a prevalence of about 1 in 1,000 [Iglesias et al., 1983] and a spontaneous mutation rate of 6.5 to 10×10^{-5} [Dalgard, 1957]. The data for the spontaneous mutation rate, obtained before the introduction of ultrasonography, probably overestimate the rate.

Our patients had ultrasonic findings compatible with PKD. None had evidence of congenital hepatic fibrosis

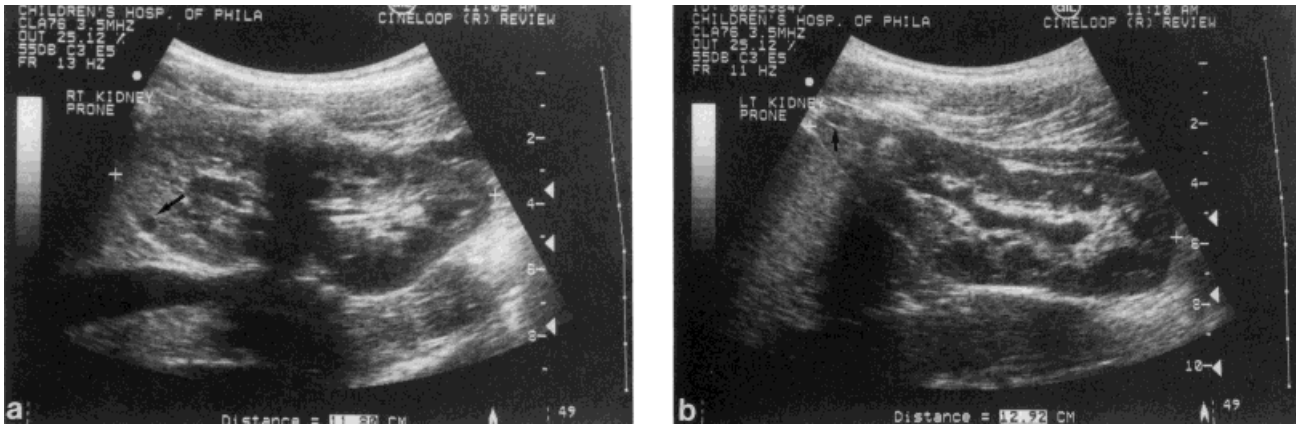

Fig. 3. **a,b:** A contrast-enhanced axial CT scan at two levels (patient 3). Note several small cysts in the right kidney (small arrows) and a large, contrast filled cystic lesion in the left kidney (large arrow). This parapelvic cyst is separate from the renal pelvis (arrowhead). However, the presence of contrast within it implied that it was connected to the collecting system.

Fig. 4. Patient 4. Sonogram at 5 months shows multiple large cysts in each kidney, however, with more cysts in the right kidney. The kidneys are enlarged. The length of the left is 7.5 cm and the right is 6.5 cm.

by ultrasonography, an invariable finding in autosomal recessive polycystic kidney disease. Furthermore, there were no signs of tuberous sclerosis, von Hippel-Lindau, oro-facial-digital type I, or Hajdu-Cheney syndromes. One of our patients had osteogenesis imperfecta type IV, and it is possible that the others had another form of cystic disease associated with disorders of connective tissue. Two had findings compatible with mild Ehlers-Danlos syndrome. Ehlers-Danlos syndrome was reported in 2 patients with apparent PKD [Lewitus, 1956; Imahori et al., 1969], a patient with autosomal recessive PKD [Mauseth et al., 1977], and patients with medullary sponge kidneys [Levine and Michael, 1967].

Somlo et al. [1993] described a kindred in which there was cosegregation of the 16p-linked form of PKD and an "overlap" connective tissue disorder similar to Marfan syndrome. Patients with this autosomal dominant disorder had aortic root dilatation, aortic and vertebral artery aneurysms with dissection, aortic valve incompetence, pectus, pes planus, joint laxity, arachnodactyly, dolichostenomelia, and high-arched palate in addition to PKD.

If our patients had a family history of PKD, thereby permitting a definite diagnosis of PKD, the occurrence of that common autosomal dominant disorder with another dominant (connective tissue) disorder would not be unlikely. On the other hand, the absence of a family history in each child, and the presence of an apparent disorder of connective tissue, raises the possibility that the cystic kidneys may be the result of the connective tissue disorder. Extra-renal manifestations of PKD, which may be the result of abnormal connective tissue, occur in many patients: liver cysts, intracranial aneurysms, cardiovascular abnormalities [Timio et al., 1992], intestinal diverticulosis, pyloric stenosis [Proesmans et al., 1982], hernias [Sedman et al., 1987], endocardial fibroelastosis [Mehrizi et al., 1964; de Chadarevian and Kaplan, 1981], and hepatic fibrosis [Cobben et al., 1990]. PKD has not been reported in patients with osteogenesis imperfecta. Our patient with osteogenesis imperfecta and polycystic kidneys had somatic asymmetry; hemihypertrophy has been reported in a child with PKD [Ritter and Siafarikas, 1976].

Studies in animals with polycystic kidney disease may not be applicable to polycystic kidney disorders in humans, and most studies in humans have been done in tissues from advanced cases of polycystic kidneys. Despite these caveats, there have been a number of interesting observations in animals and humans [Gardner, 1988; Haverty and Nielson, 1988; Gabow, 1991]. Three separate but not mutually exclusive hypotheses for the pathogenesis of cysts [Gardner, 1982, 1988] implicate increased basement membrane compliance, reversed net-water and solute movement, and partial obstruction. Gardner [1982] has discussed the possibility that a systemic defect in basement membrane results in excessive compliance and cyst formation in regions of the kidneys, liver, pancreas, spleen, ovaries, and testes, and prolapsed mitral valves, cerebral artery and abdominal aortic aneurysms, and colonic diverticulae. Arguments have been advanced in favor of [Haverty and Nielson, 1988] and against [Gardner, 1988] the compliant basement membrane hypothesis, but this is a concept that may help to explain the occurrence of polycystic kidneys in the context of syndromes in which there are defects in collagen and extracellular matrix. Normal basement membranes contain type IV collagen, laminin, heparan sulfate proteoglycan, and entactin. However, the interstitial collagens types I and III are expressed by metanephric mesenchyme prior to invasion by the ureteric diverticulum. After tubular epithelial cells have converted from mesenchyme to epithelium a switch occurs to expression of laminin and other collagens [Haverty and Nielson, 1988]. It has been suggested that this switch in extracellular matrix synthesis may be disturbed in polycystic kidneys [Haverty and Nielson, 1988]. Epithelial cells cultured from polycystic kidneys synthesize morphologically abnormal basement membranes that consist of banded collagen and proteoglycan [Wilson et al., 1986]. Studies of tissue from PKD show alterations in extracellular matrix with decreased fluorescence of antibodies to heparan sulphate-proteoglycan, normal fluorescence with antibodies to laminin and type IV collagen, and markedly increased reactivity for fibronectin in the peritubular interstitium [Carone et al., 1988]. Recent studies have shown that the 14.5 kb PKD1 transcript encodes a 4304 amino acid protein with domains that suggest that the PKD1 protein is involved in adhesive protein-protein and protein-carbohydrate interactions in the extracellular compartment [The International Polycystic Kidney Disease Consortium, 1995; Hughes et al., 1995].

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